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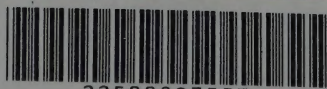
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From the Laboratories of Physiology in the Harvard Medical School

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XXVII. EVIDENCE THAT MEDULLIADRENAL SECRETION IS NOT CONTINUOUS

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One of the early theories of the function of secreted adrenin was that it exercises a continuous tonic influence on structures under sympathetic control. This theory involved the assumption that there is a continuous secretion into the blood stream. Support for the view was found in the experiments of Strehl and Weiss (1901) who reported a fall of blood pressure in rabbits immediately after closure of the adrenal vessels and a prompt rise when the vessels were opened. Kahn (1911), however, was unable to confirm these experiments—when he tied the adrenal vessels in rabbits the pressure did not fall. And Hoskins and McClure (1912) found that the procedure had no effect on the blood pressure of dogs. Other investigators, including Lewandowsky (1899), Camus and Langlois (1900) and Trendelenburg (1914) have made observations in accord with these. The evidence at hand, therefore, appears to weigh heavily against the idea that the vascular tone of blood vessels depends on a sustained discharge of adrenin.

Elliott (1904) suggested that minute amounts of circulating adrenin are necessary for the efficacy of sympathetic impulses. By test on a series of dogs, normal or deprived of their adrenal glands, that were given slow infusions of dilute adrenalin, Hoskins and Rowley (1915) were unable to demonstrate that the greater concentration of adrenin in the blood ever had the facilitating influence that had been postulated.

The observation of Aub, Bright and Forman (1922) that adrenalectomy lowers the basal metabolic rate and that intravenous infusion of adrenalin restores it has been used to support the argument for a tonic service of medulliadrenal secretion (cf. Bayer, 1929, p. 481). The argument is not compelling, however, for the reduced metabolism after adrenalectomy may be due to removal of the cortical tissue; the ability of adrenalin to raise the metabolism, under the circumstances, may be quite as independent of the adrenal cortex as it is independent of the thyroid (cf. Aub, Bright and

Forman 1922); and this ability is no more proof that adrenalectomy deprives the body of the benefits of continuous discharge of adrenin than that thyroidectomy has that effect.

The distinction which should be drawn between effects of total extirpation of the adrenals (medulla and cortex) and extirpation of the *medulla alone* is emphasized by observations on blood sugar in these two conditions. Bornstein and Holm (1922) and Banting and Gairns (1926) found that adrenalectomy caused hypoglycemia, but Frank and Isaac (1910), Kahn and Starkenstein (1911), Stewart and Rogoff (1918) and others have shown that destruction of the medullary substance does not reduce the glycemie level. It appears that the percentage of blood sugar is not dependent on a continuous supply of adrenin to the blood.

The "tonus theory" of medulliadrenal function has been attacked by others who have examined the effectiveness of sympathetic nerve impulses either directly or reflexly aroused, before and after excluding participation of the adrenals. Gley and Quinquaud (1918, 1921) have been especially vigorous in this attack. They demonstrated that vagal and depressor stimulation, as well as accelerator, had the same influence on the heart rate, and that splanchnic stimulation and asphyxia had the same effect on the blood pressure, whether the adrenal glands were present or not.

A theory of medulliadrenal function alternative to the tonus theory is that adrenin is secreted in times of special stress, when it coöperates with sympathetic nerve impulses in rendering the defense or protection of the organism more effective (cf. Cannon, 1914, 1928). There is no logical antagonism between the "tonus" theory and the "emergency" theory of the service of adrenin—adrenin might ordinarily be secreted continuously at a slow rate and the continuous output might be augmented when the sympathico-adrenal apparatus is brought sharply into action, as in emotional excitement, pain, cold, fever, asphyxia and hypoglycemia. Although the two theories might thus both be correct, however, the lack of cogent proof of continuous secretion of adrenin has tended to relegate the tonus theory to the background.

Fairly recent observations have furnished evidence which might be interpreted as favorable to a normal, continuous discharge of adrenin and which has in fact led to the inference that adrenin has a tonic effect. Stewart and Rogoff (1919) have reported a uniform unvarying secretion, which reaches the heart in sufficient concentration to exert upon it a definite action. Cannon and Rapport (1921) observed that the denervated heart in animals under ether or urethane beats considerably more slowly after removal of the adrenal glands, without, however, noteworthy fall of blood pressure. Tournade and Chabrol (1922) found that after adrenalectomy the blood pressure of a dog (A), under chloralose anesthesia, fell progressively; when the right adrenal vein of another dog (B), likewise under

chloralose, was anastomosed with the jugular of A, the blood pressure of A promptly rose; when the right splanchnic of B (previously deprived of his left adrenal gland) was sectioned, the blood pressure of A fell from 160 to 100 mm. Hg; and when the peripheral part of the cut right splanchnic of B was stimulated the pressure of A rose again to 160. They drew the conclusions that the adrenal glands by internal secretion play an undeniable rôle in the maintenance of arterial pressure, and that secretion of adrenin is continuous, due to tonic nerve impulses, as proved by the fall of blood pressure in dog A after splanchnectomy in B. Heymans (1929) confirmed these "important facts"—the pressure of an adrenalectomized dog falls progressively, and after some hours is as low as 70–80 mm. Hg, whereas it soon rises if supplied with blood from the adrenal vein of another dog. These observations, he declares, seem to demonstrate in an indisputable manner that adrenalinemia plays a continuous and not an intermittent cardio- and angiotonic rôle.

In the foregoing brief review it is noteworthy that neither Stewart and Rogoff nor Cannon and Rapport regarded the evidence that adrenin, secreted in sufficient amount to have hormonal effects on the heart, has important tonic action. Indeed, one may grant such effects as they observed, and also the effects noted by Tournade and Chabrol and by Heymans, but may still question whether they indicate a *normal* relation of medulliadrenal secretion to the functioning of the circulatory system. It is quite possible, on the basis of the emergency theory, that the manipulation, surgical interference and the excitement of entering anesthesia, that attends the acute experiment, may stimulate medulliadrenal secretion—a secretion which is quite unnatural for undisturbed animals. Thus the average figure of fifteen sets of determinations by eight different investigators for the output of adrenin from the adrenal glands in the resting state is 0.00055 mgm. per kgm. per minute (cf. Bayer, 1929, p. 551). But that amount is 10 times the minimal amount capable of producing hyperglycemia in the rabbit and 20 times the minimal amount for man (cf. Cori, 1931, p. 216). One-half that amount causes glycosuria (Trendelenburg, 1923a). Since glycosuria is abnormal this output of adrenin must be abnormal. It is obvious that this so-called "resting state," therefore, accompanied by operative disturbance of the organism, causes a considerably exaggerated medulliadrenal secretion. Indeed, as Trendelenburg (1923b) remarked, the true secretory activity in the resting animal is quite unknown.

On abolishing, by adrenalectomy or cutting the secretory nerves, the extra secretion induced under experimental conditions, characteristic atonic effects might result because the spontaneously secreted adrenin has been exerting a tonic influence. But, with that granted, is it possible that some spontaneous secretion goes on under natural, calm conditions?

Cats with denervated hearts have been observed in this laboratory for many days before and after inactivation of the adrenal medulla (removal of one, and complete denervation of the other by severance of the splanchnics and extirpation of the upper abdominal sympathetic chain) and before and after removal of the medullary portion of the remaining adrenal. The denervated heart is exquisitely sensitive to variations in the adrenin content of the circulating blood—1 part adrenin in 1,400,000,000 parts of blood causes a faster pulse (Anrep and Daly, 1925). If there is a continuous secretion of adrenin, therefore, the rate of the denervated heart should be distinctly lower after inactivation of the adrenal medulla whether by denervation or destruction.

Actual observations show that the drop in heart rate, which would indicate removal of the influence of circulating adrenin after exclusion of medulliadrenal influences, does not occur. In table 1 are assembled data already published in the paper by Cannon and Britton (1927), showing the lowest basal rates of the denervated heart in seven different animals before and after medulliadrenal inactivation. The *lowest* rates were taken from the observations made before that operation because of the readiness with which slight disturbances of the animals would cause uneasiness, and consequent discharge of adrenin and a faster pulse. There was not that danger after the operation, but, as Moore (1929) proved, protein food can raise the pulse rate, and therefore the lowest rates were selected also from among those recorded when the output of adrenin was no longer under nervous control. Comparison of the lowest basal rates before and after suppression of the medulliadrenal output by severance of the secretory nerves reveals no clear evidence in favor of continuous secretion of adrenin, at least to a degree which would have physiological effects on an organ sensitized by being deprived of its immediate sympathetic nerve supply. In two of the seven animals, 23 and 46, the lowest basal rate before was higher than it was after the operation. This might readily be due to failure to wait sufficiently long to permit the animal to become quite serene. In the other five cases the rates before were about the same as after or were somewhat lower. This is a result not favored by the conditions of the experiments, for, with the adrenal glands present and normally innervated, an accelerating effect on the denervated heart is hard to avoid.

These observations are confirmed by results derived from animals the beats of whose denervated hearts were recorded before and after exclusion of adrenin effects by *destruction of the medulla* of the remaining adrenal gland. Reference to table 2 shows that the basal heart rates do not differ consistently and to a noteworthy degree after the operation as compared with before.

The similarity of the figures reported in tables 1 and 2 indicates that after severance of the secretory nerves (in the cases in table 1) no other agency

was causing a discharge of adrenin, i.e., that denervation is equivalent to removal. It indicates also that there is no continuous "paralytic secretion" of adrenin that follows denervation, as Tournade (1931) has inferred. The failure of Tourande to remove the upper abdominal sympathetic chains, as well as the splanchnics, would explain the persistence of some discharge of adrenin, for there are secretory fibres below the splanchnic trunks (cf. Stewart and Rogoff, 1917; and Cannon, Lewis and Britton, 1926).

The results obtained by records of the denervated heart are confirmed by observations on basal metabolism. McIver and Bright (1924) found that

TABLE 1

Lowest basal rates of the denervated heart before and after medulliadrenal inactivation by nerve section

CAT NUMBER	BEFORE (DATE)	DATE ADRENALS INACTIVATED	AFTER (DATE)
23	90 (February 5)	February 11	76 (February 12)
26	90 (March 22)	March 25	104 (April 1)
27	92 (April 6)	April 6	92 (April 13)
33	116 (April 10)	April 30	122 (May 5)
38	118 (June 1)	June 4	120 (June 5)
46	124 (June 21)	June 24	100 (June 28)
49	100 (June 21)	June 24	101 (June 28)

TABLE 2

Lowest basal rates of the denervated heart before and after medulliadrenal inactivation by removal of the adrenal medulla

CAT NUMBER	BEFORE (DATE)	DATE ADRENALS INACTIVATED	AFTER (DATE)
36	104 (February 28)	March 10	102 (March 17)
83	102 (January 22)	January 26	96 (January 31)
113	102 (March 3)	March 9	96 (March 11)
265	106 (March 5)	March 6	110 (March 16)

reflex or direct nervous stimulation of medulliadrenal secretion caused an increased metabolic rate, averaging about 20 per cent above the previous level. If there is a continuous discharge of adrenin under standard basal conditions, there should be a fall of the basal rate when secretory nerves are no longer acting. Cannon, Newton, Bright, Menkin and Moore (1929) found, however, no considerable alteration of the degree of metabolism of animals after sympathetic nerve impulses were completely excluded.

In previous publications (Cannon, 1915, 1930) emphasis has been laid on the arrangement of the sympathetic division of the autonomic system for diffuse discharge,—a concept supported by the diffuse distribution

of adrenin, acting as it does, synergistically with sympathetic impulses. In short, the sympathico-adrenal system would work as a whole. As Bard (1928) has pointed out, however, the integrating center for the sympathico-adrenal system is in the diencephalon, and this center plays on subsidiary centers which may be capable of more or less independent action. Thus the vasomotor center in the medulla retains its tonic activity after being disconnected from the mid-brain. From the data presented in the foregoing pages it would appear that the tonic activity of the vasomotor apparatus does not involve a tonic activity of the adrenal medulla. When, now, the integrating center in the diencephalon becomes dominant—as in emergencies, for example, or in the need of preserving homeostasis—there would be not only increased tone of the vasomotor center, but a reinforcement of that effect by adrenin specially discharged into the blood stream. As found by Cannon and Britton (1927), quite minor activity, such as walking, may be attended by a well marked output of adrenin.

SUMMARY

Observations for and against the continuous secretion of adrenin are reviewed, and the point is made that the evidence in favor of continuous secretion has been obtained under disturbing experimental conditions.

Records taken from quiet, healthy animals, with hearts denervated for some time and thereby especially sensitized to the action of adrenin, reveal no noteworthy differences between the basal heart rates before and after the adrenal medulla was inactivated, either by denervation or extirpation (see tables 1 and 2).

Since the heart, even when freshly denervated, is, to a very high degree, sensitive to circulating adrenin, the conclusion is drawn that adrenin is not secreted continuously, but, as other experiments have shown, only in emergencies or for the preservation of homeostasis.

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